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PAPER

Photoinduced processes in nucleic acids and proteins: concluding remarks

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Light induced charge and energy transport in nucleic acids and proteins is the basis of fundamental biological processes such as photosynthesis, vision, DNA-photostability, DNA-photodamage and photosensing. This article summarises the concluding remarks given at the Faraday Discussions meeting on this topic. The specific themes arising from the meeting that are discussed herein include charge transfer in nucleic acids and proteins, excited state dynamics and topology, vibrations and dynamic disorder, proteins and charge transfer states, nanobiophotonics coupled to biomedical applications and photosynthesis.

1. Introduction

Light induced charge and energy transport in nucleic acids and proteins is the basis of fundamental biological processes such as photosynthesis, vision, DNA-photostability, DNA-photodamage and photosensing; for a review of this please see the introductory lecture given by Professor Ilme Schlichting (DOI: 10.1039/C8FD00058A). The most prominent chromophores in nucleic acids are nucleotides, retinal in rhodopsins, aromatic amino acids in proteins, and bacteriochlorophylls, carotenoids and bilins in photosynthesis. In addition there exists a variety of chromophores, often bound to specific proteins that play a role in sensing and in the regulation of DNA-expression (*e.g.* phytochromes). The relevant wavelengths of absorption for nucleotides are in the UV range (220–300 nm), while those for retinal are in the visible spectral range (300–700 nm), those for aromatic amino acids are in the UV-near UV region (220–320 nm), and those for the photosynthetic pigments chlorophyll *a*, bacteriochlorophyll *a*, bacteriochlorophyll *b* and bilins are in the ranges 300–700 nm, 300–900 nm, 300–1050 nm, 300–680 nm, respectively. Carotenoids (of which there are many) form a special class; they absorb light in the blue/green part of the spectrum (300/550 nm) to their S_2 state, while transitions to the lower energy S_1 state are forbidden or 'dark'. Excitation to the strongly allowed S_2 state determines the bright colours of carotenoids. Of course, light at wavelengths of below 300 nm is largely absorbed

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by the ozone layer, and there is a lot of light at wavelengths of above 1000 nm that is not used by vision or photosynthesis.

The absorption of a solar photon by any of these chromophores causes an electronic transition. The strongly allowed transitions (*i.e.* those with a large transition dipole moment) are typically π–π^* transitions, while the weakly allowed transitions are typically n–π^* transitions or transitions to charge transfer (CT) states that have borrowed oscillator strength from the strongly allowed transitions. This Faraday Discussions meeting for a large part dealt with the fate of such an electronic excitation, *i.e.* how it is converted into the successful isomerization of retinal in vision or in bacteriorhodopsin, how it is converted into useful charge separation in photosynthesis, how the formation of damage in nucleic acids is avoided, and how proteins with a high density of aromatic or charged amino acids deal with UV excitations.

After considering the papers that were presented during the meeting, I concluded that the meeting concentrated on the following themes, which I will discuss sequentially followed by a few general remarks:

- Charge transfer in nucleic acids and proteins;
- Excited state dynamics and topology;
- Vibrations and dynamic disorder;
- Proteins and charge transfer states;
- Nanobiophotonics coupled to biomedical applications;
- Photosynthesis.

In this discussion I will follow the roadmap outlined by Professor Ilme Schlichting in her opening lecture (DOI: 10.1039/C8FD00058A). There is a need to understand function in order to potentially manipulate it. For instance, an understanding of specificity, (fluorescence) quantum yield, side reactions and colour tuning would all help in this regard. There is also a need to characterize in detail the photophysics and photochemistry, the influence of the protein matrix, steric constraints along all steps of the reaction coordinate, and the timing/coupling dynamics of a photoreaction and protein motion, while it might also be useful to look at the generality of the mode coupling model.

It is not always easy to check the consistency of structures and spectroscopy and calculation results using other techniques. It is known that the conditions of excitation matter, *e.g.* ultrashort laser flash, nano–microsecond flash, continuous illumination, high *vs.* low intensity, temperature and excitation colour. The interplay between electronic and nuclear motions can result in complex vibronic levels, thus complicating interpretations. Calculations (QM/MM, MD) would benefit from benchmarking with ultrafast transient intermediate structures in order to find the most appropriate approach. Finally, ground state/excited state/side reactions, as well as spectroscopically/structurally silent states, need to be taken into account, while low occupancy complicates analysis (extrapolated structure factors require lots of caution and control.

The new methods that were looked at were ultrafast time-resolved X-ray spectroscopy using a free-electron laser, femtosecond two-dimensional electronic spectroscopy (2D-ES), ultrafast two-dimensional vibrational spectroscopy (2D-IR) and quantum dynamics.

2. Charge transfer

When trying to understand energy and electron transfer in nucleic acids we must realize that DNA is basically a multichromophore aggregate, for which many pathways for excited state decay and charge separation, electron/hole migration and charge recombination are potentially simultaneously possible,while all pathways are effectively in equilibrium, with the free energy differences between the various pathways being small relative to kT. The pathway that is chosen in the end will depend strongly on the environmental effects that are controlling the relative energetics of each of the possible pathways. The outcome will depend on the interplay between the fast and slow degrees of freedom (dynamic disorder) (DOI: 10.1039/C7FD00195A).[1]

One important aspect that was broadly accepted by the community of scientists present at this meeting was the fact that in densely packed structures of aromatic molecules, a DNA duplex with nucleotides at a distance of 0.3 nm or a chlorophyll-protein with a densely packed set of chlorophylls and carotenoids separated by a nm or less, charge transfer following excitation is unavoidable and ultrafast. This implies that the electronic states that are excited by light are quantum mechanically mixed with CT-states, typically leading to effective charge transfer within a few hundred femtoseconds. For photosynthesis this is precisely what you want; excitation of the photosynthetic reaction center, either directly or *via* its light-harvesting antenna, leads to a trans-membrane charge separation with a close to 100% quantum yield (QY).[2] In DNA, however, this is not what you want; you want to get rid of the UV excitation as fast as possible, but the probability of charge separation occurring is high and is ultimately most likely the cause of DNA damage (DOI: 10.1039/C7FD00205J, DOI: 10.1039/C7FD00179G, DOI: 10.1039/C7FD00195A and DOI: 10.1039/C7FD00186J).[3–8] In rhodopsins, excitation of the retinal chromophore leads to an 'intra-retinal' charge separation (DOI: 10.1039/C7FD00207F, DOI: 10.1039/C7FD00200A and DOI: 10.1039/C7FD00198C), most likely involving the surrounding amino acids and water molecules. Such a complex charge transfer state could be the precursor for isomerization.[9]

Stacked DNA, both in single strand and double strand form, shows efficient charge transfer upon UV excitation.[3–5] The charge separation occurs on a sub-picosecond timescale and subsequent recombination takes place over 2–3 ps. Studying a variety of stacked dinucleotides yielded a logarithmic correlation between the rate of charge separation and the thermodynamics, which is a characteristic of incoherent electron transfer according to the Marcus model.[10] Excitation of an unstacked DNA/polynucleotide resulted in the excitation of two neighbouring bases but did not result in charge separation. In AT alternating duplexes, UV (266 nm) excitation with a small observed yield (1.5×10^{-3}) gave rise to electron ejection, producing adenine radicals (protonated and deprotonated) and forming AT-dimers (DOI: 10.1039/C7FD00179G).

As for single-stranded DNA, in DNA duplexes upon UV-excitation two π-stacked bases will create a pair of oppositely charged radical ions, which will trigger intrastrand proton transfer (Proton Coupled Electron Transfer (PCET)), whenever the driving force allows.[11,12] As a result, UV excitation will generate a distonic ion pair in which the spin and charge are separated on the two complementary strands (DOI: 10.1039/C7FD00195A).

An unresolved question in nucleic acid spectroscopy regards the presence of excitonic states, *i.e.* excited states that are delocalized over several neighbouring chromophores/bases. Based on the dipole strengths, distances and orientations, one can easily guess the strength of the dipole–dipole interaction between neighbouring bases to be around 100 cm^{-1}. Such an interaction strength would make the electronic states excitonic and delocalized over a number of bases (4–5). Such excitonic states mixed with charge transfer states would promote ultrafast charge separation.

What could the origin and nature of UV-induced DNA damage be (DOI: 10.1039/C7FD00179G, DOI: 10.1039/C7FD00193B, DOI: 10.1039/C7FD00201G, DOI: 10.1039/C7FD00188F and DOI: 10.1039/C7FD00202E)?[13,14] In the audience there was no doubt that charge transfer between neighbouring bases possibly coupled to proton transfer is the fundamental reason for oxidative damage done to DNA by UV light. Therefore, the reactivity of DNA excited states is determined by the probability of electrons and holes formed from the CT states to escape recombination. Nucleic acids must have been designed to minimize this probability, meaning that the electrons and holes must have remained localized on neighbouring bases after charge separation. The precise reason for this localization (*e.g.* topology, coupling to selected vibrations, polaron formation) is not known. 2D-ES experiments on selected nucleic acids (DOI: 10.1039/C7FD00201G) would be highly informative for learning more about the coupling between DNA-bases in a single or double strand, coupling to the environment and the possible pathways of charge transfer. During the meeting a variety of possible DNA products were discussed; adenine radicals, UV-induced base dimerization, ionization of G-quadruplexes *etc.* The latter serves as a trap for oxidative damage in the genome and may inhibit the activity of telomerase in cancer cells after the oxidation of its guanines by UV-light.

In photosynthesis, a large light-harvesting antenna collects solar excitations (DOI: 10.1039/C7FD00190H and DOI: 10.1039/C7FD00191F.[15] The antenna consists of membrane-bound and/or membrane-associated light-harvesting pigment proteins that contain bacteriochlorophyll and carotenoids, which are often densely packed with inter-chromophore distances of less than 1 nm. In these photosynthetic antennae, carotenoid S_2 transfers energy to chlorophyll on a femtosecond timescale, but also relaxes on the same timescale to a mixed S_1 state that is still capable of energy transfer to bacteriochlorophyll on a ps timescale.[16] Keto-carotenoids are special, as in these carotenoids, following excitation, the S_2 state relaxes to a mixed S_1-ICT state, which again is active in energy transfer on a ps timescale.[17]

The resultant bacteriochlorophyll excitations are transported on a very fast timescale to the photosynthetic reaction center, also a membrane pigment–protein, that upon excitation drives a transmembrane charge separation.[18] In the photosynthetic system the collective electronic states or Frenkel excitons[19] are coupled to charge transfer states which can easily be experimentally visualized using Stark spectroscopy. The charge separation occurs within a picosecond and is strongly coupled to certain vibrations that are quasi-resonant with the relevant energy gaps. This is discussed further towards the end of this review.

3. Excited state dynamics and topology

During the meeting a variety of contributions (DOI: 10.1039/C8FD00058A, DOI: 10.1039/C7FD00207F, DOI: 10.1039/C7FD00200A and DOI: 10.1039/C7FD00198C) discussed the process of photoisomerization in rhodopsins (rhodopsin, bacteriorhodopsin, proteorhodopsin *etc.*) that occurs after photoexcitation of the retinal chromophore. The retinal is bound to the protein *via* a Schiff-base that involves a strongly bound proton between the retinal and a nearby lysine residue. The general idea is that photoexcitation of the retinal induces a structural change in the chromophore that gives rise to a rearrangement of the C–C and C=C bonds. As a consequence of this rearrangement, a typical isomerization takes place in rhodopsin around the C14–C15 bond, the proton of the Schiff base escapes and initiates the formation of the signalling state (in rhodopsin). In bacteriorhodopsin the retinal isomerizes around the C13–C14 bond and the release of the Schiff-base proton starts the proton pumping process. In both rhodopsin and bacteriorhodopsin it is believed that the so-called Hydrogen-Out-Of-Plane (HOOP) wagging modes of the retinal are excited, which drives the retinal on its excited state surface to a conical intersection (CI) where isomerization may or may not take place.[9]

A remarkable result was presented during the meeting on mutants of the *Anabaena* sensory rhodopsin (DOI: 10.1039/C7FD00200A). The native retinal isomerizes over about 700 fs, but blue-shifted mutants could be produced, some of which isomerize over about 200 fs. It is not clear to me what the mutation does to the isomerization process. I find it difficult to imagine that the HOOP dynamics were affected at all by these mutations, so it must be something else. Therefore, I challenge the rhodopsin community to figure this out. In another presentation (DOI: 10.1039/C7FD00207F) the multi-functional/state role of water molecules in the rhodopsin structure was demonstrated. Protein bound waters exhibit a dynamic structural role; they play an important role in establishing the energy landscape that the excited retinal faces before it starts to isomerize. A water molecule close to the retinal and Schiff base was shown to become disordered on an ultrafast timescale (probably a few hundred fs), and this water molecule, or better still its charges and polarizability, may play a crucial role in the ultrafast isomerization process. It would be of great interest to demonstrate explicitly what the role of water in these ultrafast events could be, *i.e.* charge transfer, proton transfer or vibronic coupling?

In a very recent paper, Haacke and coworkers[20] showed that rhodopsin isomerizes according to a unique, ultrafast mechanism that preserves mode-specific vibrational coherence all the way from the reactant excited state to the primary photoproduct. Using quantum chemical simulations, they were able to show why the observed coherent nuclear motion depends critically on minor topological/structural variations capable of inducing strong electronic effects.

In conclusion, it is not totally clear to me what actually drives the isomerization of retinal in the rhodopsins. The HOOP modes are of a much higher frequency (10–20 fs) than the timescale of isomerization (200 fs). To me it seems that there could be a lower frequency vibrational mode that resonantly couples to the isomerization, and it would be very useful to study the process of isomerization using a variety of coherent spectroscopic techniques (2D-ES, 2D-IR, 2D-

Raman) in combination with ultrafast X-ray spectroscopy and quantum dynamics calculations.

4. Vibrations and dynamic disorder

Biological matter is by definition energetically disordered. This originates from the fast local motions (fs–ps) of atomic/molecular groups, slower (ns–μs) collective motions of amino acids/nucleotides/chromophores and slow (μs–s) motions of large parts of the biomolecule, for instance the re-orientation of an α-helix in a protein. This disorder appears as a broadening of the electronic transitions (due to the ultrafast dynamics), as multi-exponential kinetics (ns) or as 'static' disorder that can be probed using techniques such as spectral hole-burning, fluorescence line-narrowing and single molecule spectroscopy.[21] All of these dynamics are due to 'unavoidable' vibrations. Molecular bonds vibrate, collective atomic groups vibrate, α-helices vibrate and DNA vibrates. Consequently, the resulting energy landscape for a single biomolecule is complex and unique. When modelling dynamic processes in biomolecules, this complexity must be accounted for.

Disorder and vibrational dynamics in relation to fundamental biological processes were barely discussed during this meeting. This is remarkable since the potential energy surfaces of DNA excited states, DNA charge transfer, retinal isomerization and photosynthetic charge separation are typically presented with large displacements relative to the charge transfer or isomerization coordinate.[9,22,23] For photosynthetic reaction centers we have shown, using 2D-ES, that the dynamics of excitation energy transfer and charge separation are closely connected to a relatively small number of vibrations, whose major role is to delocalize the electronic states and thereby speed up the energy transfer and charge separation process by one order of magnitude.[2,24,25] It would be fantastic if similar results could be obtained for DNA charge transfer and retinal isomerization. The beauty of the 2D-ES experiment is that it shows precisely the mode of coupling between the initially excited state and the product state, including possible intermediates. Coupling this kind of information with 2D-IR, 2D-Raman and fs-X-ray spectroscopy would give a big boost towards our fundamental understanding of the elementary events in photoinduced processes in nucleic acids and proteins (DOI: 10.1039/C8FD00058A).

5. Spectroscopy of proteins

During the meeting there were several presentations of new spectroscopic features observed in dense solutions of proteins (DOI: 10.1039/C7FD00183E, DOI: 10.1039/C7FD00194K and DOI: 10.1039/C7FD00203C). Essentially, it was concluded that at high concentrations of certain proteins (proteins with a large number of Lys and/or Glu residues), new absorption bands appear in the 400–700 nm spectral region, which are ascribed to CT-states, mainly between Lys and Glu and the polypeptide backbone. A computational examination of other amino acids with charged side chains (Arg, Asp and doubly protonated His) and post-translationally phosphorylated amino acids (Ser, Thr and Tyr) indicated that all of these charged amino acids could present a donor–bridge–acceptor structure. It was proposed that the appearance of these new bands reflects the secondary structure and protein modifications, and could act as another fingerprint of

protein–protein interactions. One question to be asked is what are the fluorescence properties of these 'new' bands? In case they originate from unknown CT states, Stark spectroscopy, both in absorption and emission, could be very useful for further identification.

6. Bionanophotonics

I was personally very impressed by the work discussed in the talks given by Professor Chattopadhyay (DOI: 10.1039/C7FD00192D), Dr Jayasree (DOI: 10.1039/C7FD00185A), Dr Datta (DOI: 10.1039/C7FD00197E) and Dr Joseph (DOI: 10.1039/C7FD00196G), as well as the posters that described the application of light to induce or control molecular processes at the cellular level. From what I can see, there is great future potential for the application of 'photoinduced' technologies in medicine. An excellent example of this was seen in the talk given by Dr Jayasree (DOI: 10.1039/C7FD00185A), who used gold nanorods linked to an anti-cancer drug that could be applied for both imaging and therapy.

7. Photosynthesis

The light reactions of photosynthesis include two ultrafast processes: (i) excitation energy transfer among the pigments of the light-harvesting antenna followed by (ii) trans-membrane charge separation in the reaction center. Both the light harvesting antenna and the reaction center are pigment–protein complexes associated with the photosynthetic membrane, which in plants is the thylakoid membrane. Photosynthetic bacteria make do with a single reaction center that upon excitation drives cyclic electron transfer and builds up a proton gradient, whereas in plants there are two reaction centers, Photosystem 1 (PS1) and Photosystem 2 (PS2), which operate in series. Photosystem 2, after excitation and charge separation, oxidizes water to produce molecular oxygen. Photosystem 1 reduces $NADP^+$ to NADPH following excitation. Electron transfer from PS2 to PS1 is coupled to the transport of H^+ across the membrane. The resulting H^+ gradient is used to produce ATP. ATP and NADPH are required to fix CO_2 *via* the Calvin–Benson cycle.

At this meeting there were two 'photosynthesis' contributions, both relating to bacterial photosynthesis. In the first of these talks (DOI: 10.1039/C7FD00190H) bacterial photosynthetic units were placed on electrodes, supplied with electron donors and acceptors, thus forming a bio-solar cell. These so-called RC-LH1 complexes, in which the RC is surrounded by a circular LH1 antenna, naturally contain a small protein called PufX which creates a hole in the LH1-ring. This presentation was largely dedicated to understanding the role of PufX in the performance of the bio-solar cell. It was concluded that in the absence of PufX larger currents could be generated and the bio-solar cells were more stable. It is not the idea to use such cells for current generation but instead to drive specific biochemical reactions. In the second of these talks (DOI: 10.1039/C7FD00191F) the adaptation of the light-harvesting antenna of purple bacteria to different light intensities was investigated. For the purple bacterium *Rhodopseudomonas Acidophila* strain 7050, it was found that under low light conditions the peripheral light-harvesting complex LH2 was exchanged for a more 'blue' absorbing species. The reason for this blue-shift under low-light conditions was discussed. One

possible reason is for the optimization of the efficiency of light capture by shifting the absorption spectrum of the antenna more to the visible region, not only by blue-shifting the bacteriochlorophyll absorption but also by incorporating redder carotenoids.

Finally, it is appropriate to return to the quantum-vibronic mechanism of energy transfer and charge transfer in photosynthesis. The model and conclusions are largely based on our work on the PS2RC using 2D-ES.[2,24–27] In this work we have shown that exciton transfer and charge separation are strongly coupled to a few specific low frequency vibrations. In the PS2RC (at least) two pathways of charge separation exist, one involving an exciton state largely localized on the active branch accessory chlorophyll and pheophytin, the second is an exciton state that is more or less localized on the 'special pair' of chlorophylls in the heart of the PS2RC. Our work has clearly demonstrated that these two pathways are coherently coupled through a 120 cm^{-1} vibration which shows up as a strong oscillatory cross peak in the 2D-ES frequency maps. In addition, the 'special pair' pathway is coupled to a real charge separated state *via* a 340 cm^{-1} vibration, which manifests itself *via* its coherent formation. I wish to emphasize that these coherences have nothing to do with the fact that we use ultrashort laser pulses to detect them. They are an intrinsic property of these reaction centers created by the delocalization of the relevant electronic states due to their mixing with resonant vibrations.

8. Conclusions

In conclusion, during this Faraday Discussions meeting, the participants extensively discussed the basic photophysics, photochemistry and photobiology of a variety of biological/biology related systems: DNA, rhodopsins, proteins and photosynthesis. Key considerations were given to ultrafast laser spectroscopy, charge transfer, conical intersections, topology, vibrations and functionality. It was remarkable to observe the tight connection between experiments and quantum chemical theory (hybrid QM/MM, TDDFT *etc.*). In my personal view it was a successful meeting, not only due to the quality of the presented work but also due to the participation of many young Indian scientists, including many young women. Personally I was impressed by the bridging between this area of fundamental science and possible new applications in medicine and medical therapy.

Conflicts of interest

There are no conflicts to declare.

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